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10/732,894	12/10/2003	Suhaila White	P1085US10	6903

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EXAMINER	
HIBBERT, CATHERINE S	
ART UNIT	**PAPER NUMBER**
1609	

NOTIFICATION DATE	DELIVERY MODE
06/01/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPLegal@gnf.org

Office Action Summary	Application No.	Applicant(s)	
	10/732,894	WHITE ET AL.	
	Examiner	Art Unit	
	Catherine S. Hibbert	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *3-8,14 and 16-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,9-13,15,23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *22 April 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of Application 10/732,894, filed on 10 December 2003. Please note the Examiner has changed for this Application. Claims 1-24 are pending. Claims 3-8, 14, and 16-22 are withdrawn to non-elected subject matter. Claims 1, 2, 9-13, 15, and 23-24 are under examination.

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 9 February 2007 is acknowledged. The traversal is on the ground(s) that Applicant states claim 8 should also be a linking claim. This is not found persuasive because claim 8 is clearly not generic to claims 2 and 3. Whereas Claim 2 is directed to the regulation of expression of an NF-AT responsive gene, Claim 3 is directed to testing agents for the ability to modulate cellular level of NF-AT. Claim 1 is a proper linking claim which links the Group I, drawn to a method of identifying an agent that modulates expression of an NF-AT *gene*, to Group II, drawn to a method identifying an agent that modulates the cellular level of NF-AT. Claim 8 is directed to the method of claim 1, wherein the test agent modulates the cellular level of NF-AT *polypeptide*. The expression of an NF-AT *gene* is different than, and potentially unrelated to, the cellular level of the NF-AT polypeptide.

The requirement is still deemed proper and is therefore made FINAL.

Applicant's election of the species of the nucleotide species listed in Table 1 of Accession No. BC016101, molecule No.7 in Table 1, representing CaT1 (also termed TRPV6) is acknowledged. Applicant's statement that claims 1, 2, 8-13, 15, 23 and 24 read on the elected species is acknowledged. Applicant traverses the species election and argues that the restriction requirement splits a single claim into multiple groups. Applicant's argument is not persuasive because the restriction requirement did not "split a single claim", but rather required that a species election was made for claims present in both Groups I and II. Therefore, the species requirement is still deemed proper and is therefore made FINAL.

Claims 1, 2, 9-13, 15, 23 and 24 are under examination.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

Applicant claims priority to US Provisional Application No. 60/433,389, filed 13 December 2002 is acknowledged.

Claim Rejections - 35 USC § 112 (2nd)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 9-13, 15 and 23-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The independent claims 1 and 23 recite in step (a) a "polypeptide encoded by a polynucleotide selected from the members listed in Table 1". The claims 1 and 23 are unclear because the polynucleotides listed in Table 1 refer to GenBank Accession Nos. rather than to sequences set forth in the specification. This is seen as an improper incorporation by reference, since the information required to describe and enable the required sequences is found in the Genbank database, extraneous to the application. Furthermore, since Genbank sequences are not irrevocably fixed but are corrected and updated as additional sequence information becomes available, the Genbank accession number may refer to sequences which change after the application filing date. The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to

amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973). Furthermore, if a required sequence was not set forth in the specification as filed, and was not publicly available from Genbank at the time the application was filed, the amendment will be treated as an attempt to introduce new matter (similar to attempts to incorporate essential material by reference to unpublished material). Claims 2, 9-13, 15 and 24 are indefinite insofar as they depend from claims 1 and 23.

Claims 1-2, 9-13, 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites a method comprising: (a) assaying a biological activity of an NF-AT-modulatory polypeptide encoded by a polynucleotide selected from the members listed in Table 1 or "a fragment of said polypeptide". Claim 1 is unclear because "a fragment of said polypeptide" as stated could read on a single amino acid which would produce multiple claim interpretations. Claims 2, 9-13, and 15 are indefinite insofar as they depend from claim 1.

Claim Rejections - 35 USC § 112 (1st)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 9-13, 15 and 23-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for identifying candidate agent(s) that modulate an NF-AT bioactivity comprising: (a) assaying a biological activity of an NF-AT-modulatory polypeptide in the presence or absence of a test agent, and (b) testing said agent(s) for ability to modulate an NF-AT bioactivity,

does not reasonably provide enablement for detection of a *relevant test agent* because these claims are lacking an essential comparison step whereby said bioactivity is also tested in the absence of the test agent. The invention does not allow a person skilled in the art to correlate a test agent to a *change* in the bioactivity of the TRPV6 polypeptide and therefore to identify a relevant test agent in step (a) (claims 1-2, 9-13 and 15).

In addition, the specification does not reasonably provide enablement for detection of *any* bio/activity specifically associated with the CaT1/TRPV6 polypeptide. The invention does not allow a person skilled in the art to know what potential biological

activities of the TRPV6 would be reasonable activities to be assayed or how to perform an assay to detect one of these potential TRPV6 activities (claims 1-2, 9-13, 15, and 23-24).

Furthermore, the specification, does not reasonably provide enablement for detection of *any* bio/activity. The invention does not allow a person skilled in the art to correlate any and/or all bio/activities of the TRPV6 polypeptide to being relevant to the modulation of a NF-AT polypeptide (claims 1-2, 9-13, 15, and 23-24).

In addition, while the specification may be enabling for certain cells such as epithelial cells, it does not reasonably provide enablement for *all cell types* for the method step (a) (claims 9-10 and 24). The TRPV6 is an epithelial cell Ca^{2+} channel protein which has been successfully used in oocytes and certain cell culture lines but is not found and/or expressed in *all cell types*.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h)

the level of predictability in the art (MPEP 2164.01 (a)). The following factors are relevant in the instant case:

Nature of the invention: The nature of Applicant's invention involves determination of potential agents that modulate NF-AT bioactivity by testing for agents that modulate NF-AT modulatory polypeptides and by testing agent that modulate NF-AT bioactivity. While the nature of this experiment is technologically feasible within a certain limited scope, the breadth of the claims would require undue experimentation to arrive at the desired experimental results.

Breadth of the claims: The breadth of Claims 1-2, 9-13, and 15, which recite "or a fragment thereof" would allow many options for how a skilled artisan could perform the invention because, for example, "a fragment thereof" reads on any single amino acid contained in the polypeptide sequence. However, the number of type of potential "fragments thereof" would be irrelevant to a full-length NF-AT modulatory polypeptide and there is no support in the specification that "any fragment thereof" would have any relevance to an NF-AT modulatory polypeptide.

In addition, claims 9, 10, 13, 15 and 24 recite the use of all cells. However, it has not been shown that the experiment is enabled for all cell types.

Therefore, the breadth of the claims would require undue experimentation to use this invention.

State of the Prior Art and Predictability: The state of the prior art teaches that agents can be tested in vitro and in vivo as potential candidates for modulators of NF-AT modulatory polypeptides. In addition, the state of the prior art teaches that agents can be tested in vitro and in vivo as potential candidates for modulators of NF-AT activity. The state of the prior art does not teach that any single amino acid is equivalent to an NF-AT modulatory polypeptide (see Rao and Hogan entire document).

Direction provided by the inventor and Existence of working examples: For the instant invention, the applicant does not provide direction or evidence of working examples to establish whether the invention is enabled for all cell types and all possible fragments of nucleotides encoding NF-AT modulatory polypeptides. Therefore, the skilled artisan seeking to practice the invention according to its full scope would not be able to predict which embodiments within the broad scope of the claims could be used as claimed. Therefore, the skilled artisan must experimentally determine which cells and which specific fragments would be relevant for the instant invention. For these reasons, undue experimentation would be required to use the invention as claimed.

Because of the reasons stated above, the unpredictability of the outcome of the NF-AT modulatory polypeptide expression with various cell types to determine whether the assay would be able to identify putative NF-AT modulatory agents would require undue experimentation. Therefore, the claims are properly rejected under 35 USC § 112, first paragraph, as lacking an enabling disclosure.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 9-13, 15, and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rao & Hogan (published: 8 February 2001, WO/2001/055349 "Modulation of Tolerance by Altering NFAT Signalling" [made of record in the IDS filed 22 April 2005] and further in view of Wood et al, ("l,25-Dihydroxyvitamin D3 increases the expression of the CaTI epithelial calcium channel in the Caco-2 human intestinal cell line" in BMC Physiology 2001, published 17 August 2001).

Claims 1 and 23 are directed to a method for identifying an agent that modulates an NF-AT bioactivity, the method comprising: (a) assaying a biological activity of an NF-AT-modulatory polypeptide encoded by a polynucleotide selected from the members listed in Table 1 (claim 23), or a fragment of said polypeptide (claim 1), in the presence of a test agent to identify one or more modulating agents that modulate the biological activity of the polypeptide; and (b) testing one or more of the modulating agents for ability to modulate an NF-AT bioactivity.

Rao & Hogan teaches a method comprising (a) assaying the biological activity of polypeptides listed in Table 1, or fragments of said polypeptides, such as the "RING finger protein" (p. 2, ¶ 4, line 7) in the presence of an agent, and (b) testing the modulating agent for its ability to change an NF-AT bioactivity. For example, Rao & Hogan teaches "the agent increases the activity or expression of calcineurin," by increasing the intracellular calcium concentration or increases the expression of the RING finger protein. In addition, Rao & Hogan teaches "the agent modulates (e.g., inhibits or activates) one or more of the following NFAT signaling activities:" including

activity or expression of NFAT (see especially p. 2, ¶ 2, lines 1-4 and p. 8, ¶ 1, lines 1-4).

Claims 9 and 10 are directed to the method of claim 1, and further to where step (a) occurs in a cell (claim 9), and further to wherein the NF-AT-modulatory polypeptide is expressed from said polynucleotide that has been introduced into the cell (claim 10). Claim 24 is directed to the method of claim 23, and further to wherein (a) and (b) are performed in a cell.

Rao & Hogan teaches the method of claim 1 and further teaches wherein step (a) occurs in a cell (p. 7, ¶ 5, line 1) and further to wherein the polypeptide is expressed from a polynucleotide that has been introduced into a cell (p. 15/16, ¶ 11/1, lines 1-3/1-15).

Claims 2, 11, 12 and 15 are directed to the method of claim 1, and further to wherein the step (b) NF-AT bioactivity is "regulating expression of an NF-AT responsive gene" (claim 2), to wherein the NF-AT bioactivity is "inducing expression of a second polynucleotide that is operably linked to an NF-AT response element" (claim 11), to wherein the second polynucleotide encodes a reporter polypeptide (claim 12), and to wherein the testing for ability to modulate the NF-AT bioactivity comprises contacting a cell or cell lysate with the test agent and determining ability of NF-AT to bind to a second polynucleotide that comprises an NF-AT response element in the cell or cell lysate (claim 15). Claim 13 is directed to the method of claim 12, and further to wherein the testing for ability to modulate an NF-AT bioactivity comprises: providing a cell or cell lysate that comprises the second polynucleotide that is operably linked to the NF-AT

response element; contacting the cell or cell lysate with the test agent; and detecting an increase or decrease in expression of the second polynucleotide in the presence of the test agent compared to expression of the second polynucleotide in the absence of the test agent.

Rao & Hogan teaches the method of claim 1 and further teaches wherein the NF-AT bioactivity of the method step (b) is inducing expression of a reporter polynucleotide that is operably linked to the NF-AT response element in a cell. For example, Rao & Hogan recites "the first cell also has a second nucleic acid encoding a second reporter gene operably linked to a second promoter that includes a composite NFAT-NFAT ligand" (p. 12, ¶ 11, lines 1-4).

However, Rao & Hogan differs from the invention claimed in the instant claims 1-2, 9 -13, 15, and 23-24 because, while teaching the NF-AT-modulatory polypeptide "RING Finger" protein listed in Table 1, Rao & Hogan fails to teach the specific NF-AT-modulatory polypeptide "CaT1/TRPV6" protein listed in Table 1.

Wood et al. (see especially title, abstract, lines 6-7 and Results and Discussion ¶ 1, lines1-12) teaches the CaT1/TRPV6 polypeptide.

One would have been motivated at the time the invention was made and it would have been obvious to one of ordinary skill in the art at the time the invention was made to have utilized the CaT1/TRPV6 polypeptide of Wood et al in the method taught in Rao & Hogan because Wood et al teaches the expression on CaT1/TRPV6 polypeptide in a Caco-2 human intestinal cell line which then incorporated the CaT1/TRPV6 polypeptide

into the cell membrane in order to produce active Ca++ channel. Wood et al further teaches testing the modulation of the bioactivity of the CaT1/TRPV6 channel polypeptide with the test agent I,25-Dihydroxyvitamin D3. In addition, as evidenced by Takeuchi et al (in "Nuclear Factor of Activated T Cells (NFAT) as a Molecular Target for 1alpha,25-Dihydroxyvitamin D3-Mediated Effects" in J Immunol. 1998 Jan 1;160:1:209-18), the test agent of Wood et al, termed I,25-Dihydroxyvitamin D3, was known in the prior art as a modulator of NF-AT bioactivity (see especially Takeuchi et al, title and abstract). Both Rao & Hogan and Wood *et al.* are in the same field of endeavor of NF-AT modulation and gene expression and both are directed to the same problem sought to be solved of finding test agents which modulate NF-AT activity.

Absent evidence to the contrary, one would have a reasonable expectation of success combining the teachings of the art because the use of the CaT1/TRPV6 for the purpose of testing for modulatory agents was routinely practiced at the time the teachings of Rao & Hogan and Wood *et al.* were published.

In view of the foregoing, the method of claims 1-2, 9 -13, 15, and 23-24, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC *§103(a).*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine S. Hibbert whose telephone number is 571-270-3053. The examiner can normally be reached on Monday-Friday, 7:30 AM-5:00 PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mary Mosher can be reached on 571-272-0906. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Patent Examiner: Catherine S. Hibbert

MARY MOSHER
SUPERVISORY PATENT EXAMINER
5-29-07